Hydroxocobalamin: Improved Public Health Readiness for Cyanide Disasters

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The United States is under the constant threat of a mass casualty cyanide disaster from industrial accidents, hazardous material transportation incidents, and deliberate terrorist attacks. The current readiness for cyanide disaster by the emergency medical system in the United States is abysmal. We, as a nation, are simply not prepared for a significant cyanide-related event. The standard of care for cyanide intoxication is the cyanide antidote kit, which is based on the use of nitrites to induce methemoglobinemia. This kit is both expensive and ill suited for out-of-hospital use. It also has its own inherent toxicity that prevents rapid administration. Furthermore, our hospitals frequently fail to stock this life-saving antidote or decline to stock more than one. Hydroxocobalamin is well recognized as an efficacious, safe, and easily administered cyanide antidote. Because of its extremely low adverse effect profile, it is ideal for out-of-hospital use in suspected cyanide intoxication. To effectively prepare for a cyanide disaster, the United States must investigate, adopt, manufacture, and stockpile hydroxocobalamin to prevent needless morbidity and mortality.

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PUBLIC HEALTH THREAT

Cyanides, in both solid and gaseous forms, are valuable ubiquitous compounds in American industry. Many chemical processes and manufacturers take advantage of the highly reactive characteristics of the cyanide ion (CN^-). During mining operations, cyanide is used in the extraction of gold and silver from mineral ores, and a similar process is used to recover silver from recycled photographic materials.[1] Producers of plastics, pigments, and dyes often use and store vast quantities of cyanide gasses and salts.[1] Cyanides are also used as fumigant pesticides.[1-3]

In 1993, The National Toxic Release Inventory detailed cumulated release of 3,291,307 pounds of cyanide from some 175 sites, but by 1997, the top 100 sites had released a total of over 4,513,410 pounds of cyanide.[1,4] Although these releases in themselves are not necessarily a public health threat, they do emphasize the scale of our predicament. The Union Carbide Pesticide Plant disaster in Bhopal, India, provides us with a horrific example of a massive industrial incident. Located in the densely populated city of 900,000, the fire and subsequent leak released almost 25,000 kg of methyl isocyanate and its combustion products. The methyl isocyanate and cyanide compounds, along with many other combustion products, caused between 1,800 and 5,000 deaths and almost 200,000 injuries.[5] The United States is just as active in the use of cyanide compounds for commercial operations.

According to the US Department of Transportation Web site, trucks, trains, ships, and planes move 4 billion tons of hazardous materials annually. They also estimate that over 500,000 hazardous material shipments transpire on a daily basis. Although most bulk transportation takes place on rail lines or within ships, almost all the metropolitan areas in the United States are geographically intimate with railways or ports. This means that nearly all bulk hazardous materials shipments travel through major municipal areas. From 1990 to 1996, the US Department of Transportation recorded a mean hazardous material transportation accident rate of 12,115 incidents per year. In 1996 alone, there were 11,797 highway incidents and 1,086 railway incidents. The death toll for 1996 hazardous materials incidents was 120 lives.[6]

During 1992 in Washington State, there were 512 incidents resulting in 102 symptomatic exposures. In 80% of these incidents, at least one exposed individual was transported to a medical care facility. One cyanide-specific motor vehicle crash alone resulted in the transport and treatment of 11 individuals from symptomatic exposure.[7] Data from Massachusetts reveal a similar trend in cyanide release as related to transportation accidents.[8]

In recent years, the threat of terrorism in the United States has become increasingly real and alarming. The bombings of the Alfred P. Murrah Federal Building in Oklahoma City and the World Trade Center in New York City are poignant examples of this problem.[9,10] The deliberate release of chemical agents by terrorists is no longer a threat but a reality. In 1995, the actions of terrorists caused over 5,500 casualties and 12 deaths from the deliberate and systematic release of the nerve agent sarin.[10,11]

Although not well covered in the popular press, cyanide compounds were also found in the Tokyo subway attack and possibly in the World Trade Center bombing. Cyanide gas precursors, acid and cyanide salt, were apparently discovered in Tokyo subway bathrooms after the sarin incident.[12] The trial transcripts from the World Trade Center bombing revealed that cyanide was loaded in addition to the explosive. The resultant detonation destroyed the toxicant and prevented contamination of the structure.[10] (However, use of cyanide in the World Trade Center bombing is now also disputed.)

Intentional cyanide poisonings are not always associated with terrorism. In 1984, 7 Chicago residents were killed after ingesting cyanide-laced Extra Strength Tylenol capsules.[3] Although later linked to a murder plot, the fear of poisoned capsules pulled Tylenol off the shelves and cost the company millions of dollars.

Fires of residential and commercial buildings are well known for producing cyanide toxicity in victims. Plastics, rugs, silks, furniture, and construction materials all contain cyanogenic compounds. Cyanide generation occurs during pyrolysis of these compounds. Several authors have demonstrated a significant correlation between blood cyanide levels and carbon monoxide concentrations in fire victims.[13] Up to 35% of all fire victims may have toxicologically significant levels of cyanide.[14] Cobb and Etzel[15] studied the epidemiology of carbon monoxide–related deaths in the United States. They reviewed death certificates from 1979 to 1988 and found that 15,523 victims died from carbon monoxide poisoning associated with structure fires. This figure only accounts for the deaths from carbon monoxide and tells us nothing about the numbers of victims exposed. Given a well-documented relationship between carbon monoxide and cyanide blood levels, it is appropriate to assume that many of these victims also had cyanide intoxication. It has also been suggested that cyanide intoxication may have a large role in the mortality of smoke inhalation victims.[16] Canine models have shown that carbon monoxide intoxication alone has little effect on hemodynamic parameters and metabolic functions, but the addition of cyanide produces severe dysfunction.[17]

PATHOPHYSIOLOGY

Cyanide or its ion, CN^-, enters the body through inhalation, ingestion, or skin and mucous membrane absorption. After it is absorbed, it is rapidly distributed and has an estimated volume of distribution of 1.5 L/kg. The majority of cyanide is protein bound (60%).[18] Rhodanese is a naturally occurring enzyme that metabolizes CN^- to thiocyanate by using thiosulfate as a precursor molecule.

The kidneys eliminate thiocyanate. Human beings can tolerate low levels of cyanide exposure without harm.

Cyanide is described as a cellular toxin because it inhibits aerobic metabolism. It reversibly binds with cytochrome oxidase and inhibits the last step of mitochrondrial oxidative phosphorylation. This inhibition halts carbohydrate metabolism from the citric acid cycle, and intracellular concentrations of adenosine triphosphate are rapidly depleted.[12,19-21] When absorbed in high enough doses, respiratory arrest quickly ensues, which is probably caused by respiratory muscle failure. Cardiac arrest and death inevitably follow.

The ingested lethal dose of hydrogen cyanide for an adult human being is an estimated 50 mg.[18] For inhalation exposure, the median lethal concentration time is around 2,500 to 5,000 $mg \cdot min^{-1} \cdot m^{-3}$. The median lethal dose for skin contamination is believed to be 100 mg/kg.[12]

With the inhalation of high-concentration hydrogen cyanide (300 mg/m^3), symptoms become rapidly obvious. The victim's skin is a flushed reddish pink, and tachypnea, tachycardia, and nonspecific central nervous symptoms appear. Stupor, coma, and seizure immediately precede respiratory arrest and cardiovascular collapse. Death shortly occurs.

In moderate and severe cyanide intoxication, the clinical outcome is dependent on the severity of exposure and the delay in treatment. Cerebral hypoxia, with its subsequent encephalopathy, is common in severely poisoned casualties.[22]

CURRENT STATUS OF CYANIDE ANTIDOTE IN THE UNITED STATES

For years, the well-known Cyanide Antidote Kit (CAK; Lilly) has been the only commercially available antidote approved by the US Food and Drug Administration (FDA) for treatment of cyanide poisoning in the United States. Lilly has discontinued its production. Today, the CAK is available from one source, Taylor Pharmaceuticals (formerly Pasadena Research Laboratories).

The CAK contains amyl nitrite pearls, sodium nitrite solution (10 L of a 30 mg/mL concentration), and thiosulfate. The amyl nitrite pearls are crushed and introduced into the reservoir of the mechanical ventilation device. This agent serves as a temporizing measure before intravenous administration of the sodium nitrite. Sodium nitrite rapidly induces the formation of methemoglobin in red blood cells. A methemoglobin level of 20% to 25% is desirable. Because cyanide has higher affinity for methemoglobin than the cytochrome oxidase enzyme, it rapidly complexes with methemoglobin, releasing cytochrome oxidase to resume normal cellular respiration. Thiosulfate is then intravenously injected. In turn, thiosulfate has a higher affinity for cyanide than methemoglobin. Thiosulfate reacts with CN^- to form thiocyanate. Thiocyanate is nearly nontoxic and rapidly secreted by the kidneys.

The CAK itself is not without its own inherent toxicity and adverse effects. Sodium nitrite can cause severe hypotension.[27] High thiocyanate levels (>10 mg/dL) have been associated with vomiting, psychosis, arthralgias, and myalgia. Anaphylaxis is a rare event.[18] The most concerning factor about the CAK is the production of methemoglobin. This prevents its indiscriminate use in all but confirmed cyanide intoxications and may serve to delay life-saving intervention. Fatal methemoglobinemia from an iatrogenic overdose of sodium nitrite has claimed at least one child who consumed a sublethal dose of cyanide.[28] The pharmaceutical induction of methemoglobinemia is also contraindicated in those smoke inhalation victims who already have carboxyhemoglobinemia. The combination of carboxyhemoglobinemia and methemoglobinemia reduces the oxygen-carrying capability of the blood below life-sustaining levels.[14,16]

Multiple authors have surveyed most regions of the United States and repeatedly demonstrated a crisis of inadequacy.[10,23-25] In most of these surveys, the authors defined adequate supplies of the CAK as the amount necessary to treat a single 70-kg patient (ie, one kit). Pharmacists and hospital administrators self-reported the quantities of kits on hand. Fifteen percent to 25% of hospitals surveyed lacked the ability to treat even a single patient with the CAK because of their failure to keep the kits available.[23-25] Chyka and Conner[26] published findings that suggested that 81% of Tennessee hospitals could not treat two 70-kg patients because of inadequate supplies.[26] On the basis of these data, it is easy to extrapolate that a major metropolitan center with 20 hospitals may have only 16 CAKs for the entire population of the city. Not only is the quantity completely inadequate to treat even a limited mass casualty situation, the kits would be widely dispersed throughout the community and unavailable for rapid use.

HYDROXOCOBALAMIN

Hydroxocobalamin has been recognized as an antidote for cyanide toxicity for more than 40 years.[29-31] It is in active use in France as an antidote for cyanide intoxication. Excellent data about its efficacy, safety, and adverse

reactions are available. Hydroxocobalamin (vitamin B_{12a}) is a precursor molecule of cyanocobalamin (vitamin B_{12}) and is currently approved by the FDA. It is the drug of choice for the treatment of pernicious anemia, and several hundred thousand doses are administrated annually. Vitamin B_{12a} is available over the counter as a food supplement, which is taken by millions of people without reported harm. However, hydroxocobalamin is rarely used in the United States as a cyanide antidote.[32]

Hydroxocobalamin binds with cyanide on an equimolar basis to form cyanocobalamin (vitamin B_{12}) and thereby detoxify cyanide. It appears that 5 g of the antidote will effectively treat patients intoxicated with up to 40 μmol/L without the need for an additional dose.[33,34]

Although many authors have suggested that hydroxocobalamin's mechanism of action is the binding of cyanide in the intravascular space, Astier and Baud[35] incubated human fibroblasts in vitro with radiolabled cyanide and then hydroxocobalamin. After incubation, obvious intracellular detoxification took place, with an intracellular/extracellular ratio of 158:1. This suggests that in vivo hydroxocobalamin penetrates cyanide-laden cells and detoxifies the agent at the site of injury. This contrasts with methemoglobin, the mainstay of nitrite therapy, which remains within the erythrocyte so that cyanide must redistribute to the intravascular space to be detoxified; the clinical implications of this remain unclear.

de la Coussaye et al[36] reported on the pharmacokinetics in conscious dogs dosed with 70 mg/kg body weight hydroxocobalamin (equivalent to a 5-g dose in adult human beings). At this dose, the elimination half-life was 7.36 ± 0.79 hours, with a volume of distribution of 0.49 ± 0.10 L/kg and a total clearance of 0.58 ± 0.11 L/h. Two human pharmacokinetics studies of hydroxocobalamin have been published; both used the 5-g dose. The first study, that evaluating healthy subjects, reported an elimination half-life of 1.58 to 5.40 hours and a volume of distribution of 0.19 to 0.30 L/kg.[37] Hydroxocobalamin pharmacokinetics in smoke inhalation victims was reported in 1996 by Houeto et al.[34] They found an elimination half-life of 26.2 ± 2.7 hours, with a volume of distribution of 0.45 ± 0.03 L/kg and a total clearance of 0.83 ± 0.07 L/h. All 3 authors suggest a 2-compartment model. Clearly, further investigation into this subject is necessary.

Transient pink discoloration of the mucous membranes, skin, and urine occurring almost immediately after doses in the 4- to 5-g range is present in almost every patient who receives hydroxocobalamin. This effect fades within 24 to 48 hours after administration and coincides with half-life of the drug from urinary elimination.[34,37,38]

Rare anaphylactic reactions have been reported in patients receiving chronic intramuscular injections for pernicious anemia.[39-41] This extremely rare reaction has been associated only with chronic use and has never been reported with single-use high-dose therapy. Besides being chronically sensitized to hydroxocobalamin, these patients also had significant comorbid conditions in addition to anemia. One high-dose animal trial did, however, report self-resolving generalized urticaria without cardiovascular compromise in a single dog.[42]

Tachycardia and hypertension have been occasionally reported in high-dose therapy, and at least one author suggested that it might limit the usefulness of hydroxocobalamin.[12] However, Riou et al[42,43] studied the hemodynamic effects of hydroxocobalamin in conscious dogs and found no evidence of alteration of heart rate, mean arterial pressure, left ventricular end-diastolic pressure, or electrocardiogram tracings. A self-limited vasoconstrictive effect has been confirmed. This hypertensive effect in dogs was also described in healthy human smokers who were given 5 g of hydroxocobalamin intravenously. The individuals studied had a mean increase of systolic blood pressure from 13.6% to 23% and a mean increase of diastolic blood pressure from 25.9% to 36%. All patients presenting with increases in blood pressure had resolution and returned to baseline within 48 hours of administration. None of the subjects required medication for hypertensive control.[37]

Curry et al[38] demonstrated the in vitro effects of high-dose hydroxocobalamin on various laboratory tests. Laboratory tests that were among the most significantly affected by hydroxocobalamin administration were reportedly those measuring levels of aspartate aminotransferase, bilirubin, creatinine, and magnesium. Increases in bilirubin and magnesium values were proportional to increasing hydroxocobalamin concentrations. The serum of values of aspartate aminotransferase and creatinine were inversely proportional to the increase in blood hydroxocobalamin concentrations. Another study reported interference with the assay methodology for creatine kinase.[44] Forsyth et al[37] reported in vivo alterations in white blood cell count, partial thrombin time, and serum sodium, bilirubin, and creatinine values, but the authors did note that most of the changes remained within normal reference ranges, and any significant changes had resolved by 48 hours.

Hydroxocobalamin has been tested in mice, guinea pigs, and dogs without apparent ill effect. There is excel-

lent experimental evidence to support both the safety and antidotal effect of high-dose hydroxocobalamin in the prevention of morbidity and mortality of cyanide intoxication in experimental animals.[29,42,45-47]

Several human trials have been conducted in the United States with hydroxocobalamin, but the most definitive human trials have taken place in France. Cottrell et al[48] authenticated the value of hydroxocobalamin in the prevention of nitroprusside-induced cyanide toxicity. Nitroprusside is a valuable antihypertensive agent used in the intensive care setting, but its use is often limited by the toxic effect of cyanide production. A number of cyanide-related deaths have even occurred. By means of the administration of low-dose hydroxocobalamin intravenous drips during the nitroprusside infusion, the investigators were able to prevent the cyanide-associated toxicity of nitroprusside. A more recent review article by Zerbe and Wagner[49] has supported the findings of Cottrell et al.

Hydroxocobalamin's effectiveness was also demonstrated among human subjects who smoke tobacco. Smokers' blood levels of cyanide were compared before, on completion of the hydroxocobalamin infusion, and 1 hour after termination of the medication. Their mean blood cyanide levels (originally 53% to 56%) decreased by 59% to 87% at 1 hour after infusion. The placebo control group had a mean decrease of 9% and 14%, respectively, for termination and 1 hour after termination blood values.[50] Clearly, hydroxocobalamin decreases blood cyanide levels.

In 1987, Hall and Rumack[51] reviewed several case reports detailing the French experience from 1970 to 1984. They reported on 10 cases in which hydroxocobalamin-sodium thiosulfate combination therapy was used in patients who were severely intoxicated with cyanide. Two cases were treated with only hydroxocobalamin-sodium thiosulfate and recovered despite cardiovascular collapse. Four patients in severe distress received nitrite and dicobalt-ethylenediaminetetraacetic acid (EDTA) treatments without improvement but showed "immediate" improvement and recovery when hydroxocobalamin sodium thiosulfate was administered. Two patients received dicobalt-EDTA hydroxocobalamin-sodium thiosulfate with full recovery. Two other patients in whom treatment with dicobalt-EDTA failed also had no response to hydroxocobalamin-sodium thiosulfate treatment and later died.

RECOMMENDATIONS

Unfortunately, as is the case for most chemical disasters, the United States is woefully unprepared for a major cyanide disaster. Although several authors have called for the stockpiling of antidotes, there has been little or no change in our nationwide readiness.[10,52,53] The situation is complicated by the perception that cyanide intoxication is a rare event, but cyanide comorbidity of smoke inhalation appears to be underreported in the United States.

Our readiness for cyanide disaster is further complicated by the lack of an out-of-hospital antidotal therapy for the treatment of cyanide intoxication. The nature of severe-to-moderate cyanide intoxication demands rapid and definitive identification and intervention by out-of-hospital medical personnel to reduce morbidity and mortality. This would require the ability to manually or mechanically ventilate the intoxicated patient and provide an antidote at the disaster site. In addition to the fact of its limited availability, the CAK is itself too toxic for out-of-hospital providers to safely administer. Furthermore, the CAK is quite expensive to purchase (US $275 average wholesale price).

Hydroxocobalamin may be the solution to the problem. It is an efficacious, safe, and easy to use medication. It represents what may be an ideal medication for both in-hospital and out-of-hospital care of cyanide intoxication. The Cyanokit, available in both 2.5-g and 5-g doses, is in current production by Orphan Europe SARL (Immeuble, Paris, France). Unlike the 1-mg/mL concentration found in the United States, the French are packaging their solution in a 5-g/100-mL vial. This highly concentrated formulation prevents the need for large (5,000 mL) volumes of infusion that would be necessary to achieve antidotal dosage with the FDA-approved concentration. This antidote is used in in-hospital and out-of-hospital settings in France. It is routinely given to smoke inhalation victims by out-of-hospital emergency medical providers.

US academic and institutional researchers should actively promote investigations that may further the acceptance of hydroxocobalamin as indicated for the treatment of cyanide poisoning. Such studies solely dedicated for the purpose of research may not require investigational new drug approval. Commercial sponsors should consider investigational new drug application for the development of a more highly concentrated dose of hydroxocobalamin to be used as a cyanide antidote. European safety and formulation data, years of foreign clinical experience, and existing animal data could facilitate and lessen the expense of a new drug application in the United States. There may also exist possibilities for the provision of application fee waivers in view of the potential implication for terrorism preparedness and national security. In addition, the potential for a worldwide market may now exceed any prior level of demand.

A placebo control study of the benefits of hydroxocobalamin administration to smoke inhalation and burn victims is also indicated. Evidence of a statistically significant beneficial effect could represent a call for change in the standard of care for smoke inhalation. If proven effective, hydroxocobalamin would become more marketable to the pharmaceutical industry.

To prepare the United States for cyanide disasters, we should consider investigation, manufacture, and stockpiling of an effective and safe antidote for use by our hospitals and out-of-hospital emergency medical services personnel. To do this, we must consider safe and inexpensive alternatives to the existing therapy. Because the current antidote (CAK) is unsuitable for out-of-hospital use and quite expensive, it will probably prevent any realistic chance of stockpiling and thereby prevent any real readiness for a disaster. This makes an alternative antidote an absolute necessity. Hydroxocobalamin may be the best choice.

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